,I HEREBY CERTIFY THAT THIS CORRESPONDENCE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE AS FIRST CLASS MAIL IN AN ENVELOPE ADDRESSED TO: COMMISSIONER FOR PATENTS, P.O. BOX 1450, ALEXANDRIA, VA 22313-1450, ON THE DATE INDICATED BELOW.

BY: _____ Date: July 12, 2006

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Patent Application of: Winston T. K. Cheng et al.			
Conf No: 8832		Group Art Unit:	1632
Appln. No.:	10/820,777	Examiner:	Paul. T. Dowell
Filing Date:	April 9, 2004	Attorney Docket No.:	683884-2US

Title: METHOD FOR PRODUCING BIOLOGICALLY ACTIVE HUMAN FACTOR VIII IN THE MILK OF TRANSGENIC ANIMALS DRIVEN BY MAMMARY-SPECIFIC EXPRESSION CASSETTES

DECLARATION OF CHUAN-MU CHEN UNDER 37 C.F.R. § 1.132

I, Chuan-Mu Chen, hereby declare as follows,

1. I am a joint inventor of the patent application No. 10/820,777 (hereinafter '777 application). As a Molecular Embryologist and a Professor of Department of Life Sciences and Institute of Biomedicine at the Chung Hsing University. My current research focuses on the area of gene regulation studies in preimplantation embryo genomes and tissue-specific gene expressions of transgenic animal generations for bio-pharmaceutical productions. I am also interested in researches in elucidating the alternative epigenetic modification of DNA methylation change in cancer biology and developmental biology. I have published more than 35 papers and 13 patent applications in embryonic research and cancer research fields ((see Annex I). I have been a reviewer for the Taiwan Government National Science Council (NSC) Research Program since 1998, and also an oversea reviewer for the Research Grants Council (RGC) of Hong Kong since 2002. Together with a leading Taiwan transgenic cloned animal research team, I have earned an honor of Taiwan President Agriculture Innovation Award in 2006.

2. In light of my background and my professional experience, I am qualified to clarify the enablement of the invention addressed in the '777 application. I believe based on my professional knowledge and experience that the recombinant human clotting factor VIII (FVIII) and B-domain deleted human FVIII, which were successfully expressed in the transgenic mice, goats and pigs in accordance with the invention, would also be successfully expressed in the transgenic cow. In the mammary gland-expressing cassette for exogenic human FVIII gene regulation, several original designs have been made in accordance with the '777 application. Cow is a typical mammal and it is expected that the mammary gland-expressing cassette can be successfully expressed in cow. Accordingly, transgenic cow with recombinant human FVIII and B-domain deleted FVIII should be within the scope of the '777 application.

3. I am explaining the advantages and features of the production of rFVIII protein in the milk of transgenic animals according to the invention as follows:

A. In the '777 application, the **stringent lactating-specific regulation sequence (2.0-kb) of alpha-lactalbumin gene from a high milk-producing Holstein cow** (as described in the "Transgenesis Constructions" section in the '777 application) with essentially transcriptional binding motifs, such as MPBF, ERRE, YY1, and MGF motifs was identified and first used in transgenic animals.

B. In accordance with the '777 application, the transgenic animals as obtained had **extremely high secretion signaling for leading rFVIII protein secreted into mammary alveoli**, by constructing **a nucleotide sequence of an artificial alpha-lactalbumin of 19-aa signal peptide sequence (SEQ ID: No. 1 and 13) or a nucleotide sequence encoding an artificial alpha-S1-casein of 15-aa signal peptide sequence (SEQ ID: No. 2 and 14)**, instead of the human *FVIII* gene encoding the intrinsic 19-aa signal peptides of human *FVIII* mentioned in the prior art references (as cited in the office action).

C. In the '777 application, the **germline-transmitted transgenic mice, goats, pigs and cows harboring both full-length human FVIII and B domain-deleted rFVIII (SEQ ID: No. 15) in their genomes**, were and are expected to be successfully generated, which guaranteed a high level of rFVIII protein synthesis in the lactating mammary gland of the transgenic animals; and

D. In accordance with the '777 application, the transgenic animals as obtained had a **relatively high secretion of rFVIII protein in the milk of the transgenic animals, wherein the concentration of rFVIII protein (> 50 μg/mL) was 250-fold higher** than that of normal

human plasma (0.2 μg/mL), and **the clotting activity was 13-fold higher** than that of normal human plasma.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the '777 Application or any patent issued thereon.

Respectfully submitted,

June, 6, 2006 By: Chuan-Mu Chen

(Date) Chuan-Mu Chen

ANNEX I

Research Articles

1. K. Y. Chong, **C. M. Chen**, and K. B. Choo, 1993. Post-hybridization recovery of DNA from membrane filter for polymerase chain reaction (PCR) amplification. ***BioTechniques*** 14: 575-578. (SCI)

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13. W. T. K. Cheng, B. C. Chen, S. T. Chiou, and **C. M. Chen*.** 1998. Use of nonautologous microencapulated fibroblasts in growth hormone gene therapy to improve growth of midget swine. ***Hum. Gene Ther.*** 9: 1995-2003. (SCI)

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